PATENT CASE No. **CD1613K**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|
| In re Application of: **Frank X. Chen, et al.** | |
| | Examiner: **Evelyn Mei Huang** |
| For Patent For: | Group Art Unit: **1625** |
| **AN ENANTIOSELECTIVE PROCESS** | Date: **June 10, 2005** |
| Serial No.: **10/676,212** | |
| Filed: **10/01/2003** | |

Schering-Plough Corporation
Kenilworth, New Jersey 07033-0530

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop: Amendment

**AMENDMENT – DOCUMENT 2**

Sir:

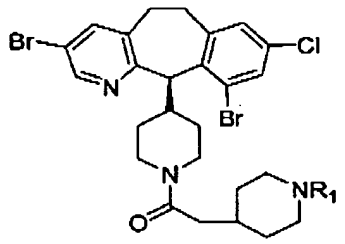
This Document should be considered after consideration of Document 1 (submitted herewith).

In view of the following amendments and remarks, reconsideration and favorable action on the claims is respectfully requested.

The amended, cancelled, new and original claims follow.

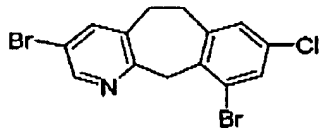
**IN THE CLAIMS**

1. (CURRENTLY AMENDED) An enantioselective process of preparing a compound represented by formula **VI**



**VI**

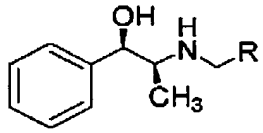
wherein $R_1$ is H or a protecting group;
which comprises contacting a compound represented by formula **V**



**V**

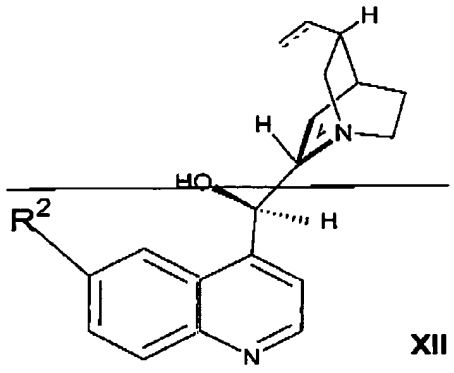
in an inert organic solvent with at least about an equivalent amount of each of:

(i) a chiral amino alcohol represented by the formula **XI**

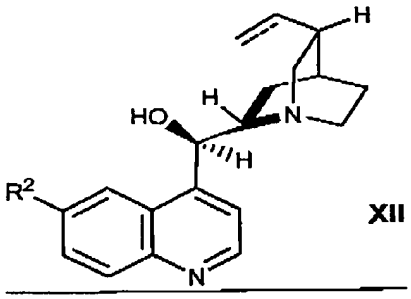


**XI**

wherein R is an aryl, akylaryl, alkoxylary, arylaryl, heteroaryl, or polycyclic aryl group, or formula **XII**



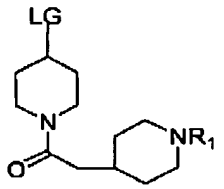
XII



XII

wherein in formula **XII**, the dotted line represents an optional second bond and wherein $R^2$ is selected from alkoxy, alkoxyalkyoxy, aryloxy, arylalkoxy, and $NR^AR^B$, wherein $R^A$ and $R^B$ are independently alkyl or aryl, and $R^2$ is optionally substituted by one or more alkoxy groups;

(ii) a compound represented by formula **X**



**X**

wherein LG is a leaving group ,and said leaving group is a sulfonate, and $R_1$ is H or a protecting group; and

(iii) an organic ether or amine additive, wherein the organic ether or amine additive is 2-isopropylamine, tetramethylethylenediamine or N-ethylaniline, N-phenyl, N-benzylamine or N-phenyl, 1-or 2-naphthyl amine or mixtures thereof to form a reaction mixture;

then adding to the reaction mixture at least an equivalent amount of a non-nucleophilic strong base in an organic solvent, wherein the non-nucleophilic strong base is a lithium base selected from the group consisting of lithium diisopropyl amide, lithium N-butyl-N-phenyl amide, lithium bis(trimethylsilyl)amide, and lithium N-ethyl,N-phenyl amide, and optionally adding an equivalent amount of water or a $C_1$ - $C_3$ alcohol to produce the compound represented by formula **VI**.

2. Cancelled.

3. Cancelled.

4. Cancelled.

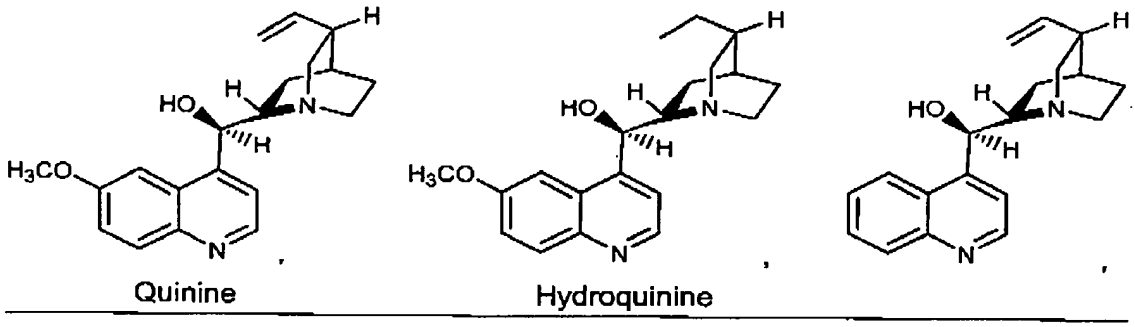
5. (ORIGINAL) The process of claim 1 wherein the reaction is conducted under an inert atmosphere.

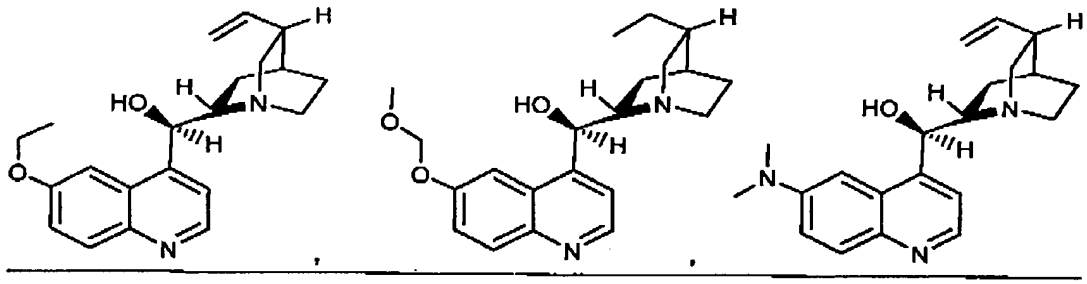
6. (ORIGINAL) The process of claim 1 wherein water is added to the reaction mixture comprising compound **V**, the chiral amino alcohol, compound **X**, the organic additive, and the non-nucleophilic strong base.

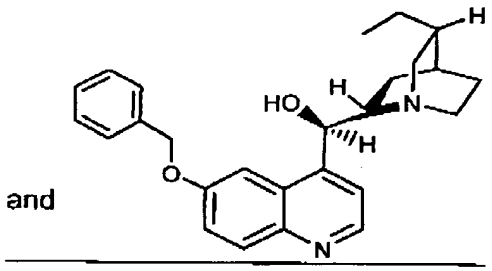
7. (PREVIOUSLY PRESENTED) The process of claim 1 which further comprises adding about 0.5 to about 1.2 equivalents of water to the reaction mixture comprising about 0.7 to about 1.2 equivalents of each of compound **V**, about 1.0 to about 2.5 equivalents of the chiral amino alcohol, compound **X**, about 1.0 to about 3.0 equivalents of the organic additive, and about 0.9 to about 1.1 equivalents of the non-nucleophilic strong base.

8. (CURRENTLY AMENDED) The process of claim 7 which further comprises adding about 1.8 to about 2.4 additional equivalents of the non-nucleophilic strong base , in two approximately equal portions, to the resulting reaction mixture formed by the ~~the~~ process of claim 7.

9. (CURRENTLY AMENDED) The process of claim 1 wherein the chiral amino alcohol is ~~quinine or a quinine derivative of formula XII~~ selected from the group consisting of:






10. (PREVIOUSLY PRESENTED) The process of claim 1 which further comprises treating the compound of formula **VI** wherein $R_1$ is a protecting group with sufficient aqueous acid to produce a reaction mixture comprising the compound of formula **VI** wherein $R_1$ is H, and adding to the reaction mixture at least about an equivalent of a chiral organic acid to form an acid addition salt, and then isolating the acid addition salt and then contacting the resulting isolated acid addition salt with sufficient base in a solvent to form the compound of formula **VI** wherein $R_1$ is H.

11. (ORIGINAL) The process of claim 10 wherein the chiral organic acid is N-α-(tert-butoxycarbonyl)-L-asparagine, di-p-toluoyl-L-tartaric acid, N-(tert-butoxy-carbonyl)-L-proline, (S)-(-)-2-hydroxy-3,3-dimethylbutyric acid, N-acetyl-L-phenylalanine or (1R)-(+)-camphanic acid.

12. (ORIGINAL) The process of claim 1 wherein the chiral amino alcohol is quinine.

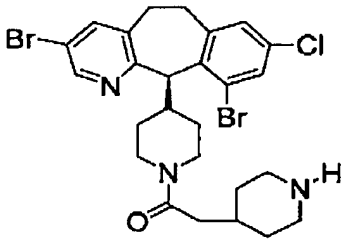
13. (ORIGINAL) The process of claim 1 wherein in compound **X**, LG is mesylate, and $R_1$ is t-butoxycarbonyl.

14. Cancelled.

15. Cancelled.

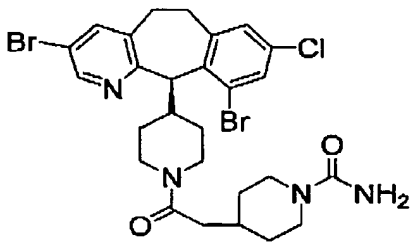
16. Cancelled.

17. (PREVIOUSLY PRESENTED) The process of claim 1 further comprising contacting a compound represented by the formula **VI**




**VI**

with an effective amount of sodium cyanate, and an effective amount of sodium carbonate in a water miscible organic solvent comprising an effective amount of water to form the compound represented by the formula **I**

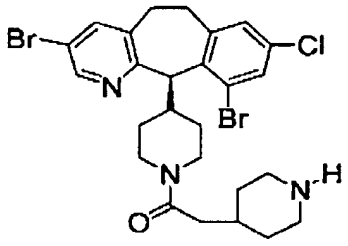



I

18. (PREVIOUSLY PRESENTED) The process of claim 17 which further comprises contacting the compound represented by the formula I with a solvent mixture comprising tetrahydrofuran, ethyl acetate and water for a time sufficient to produce the compound represented by the formula I, in a substantially chemically pure form.

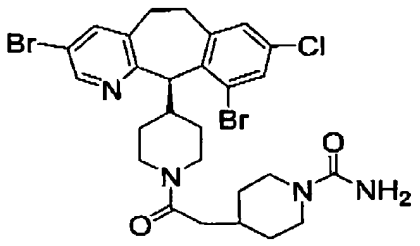
19. Cancelled.

20. (CURRENTLY AMENDED) The process of claim ~~17~~ 1 further comprising contacting a compound represented by the formula VI




VI

with about 1 to about 6 equivalents sodium cyanate, and about 0 to about 1 equivalents of sodium carbonate in a water miscible organic solvent comprising an effective amount of water to form the compound represented by the formula I




I

~~wherein the equivalent amount of sodium cyanate was about 1 to about 6 equivalents, and the equivalent amount of sodium carbonate was about 0 to about 1 equivalents~~ .

21. (PREVIOUSLY PRESENTED) The process of claim 20 wherein the equivalent amount of sodium cyanate was about 2.2 to about 2.4 equivalents, and the equivalent amount of sodium carbonate was about 0.1 to about 0.3 equivalents.

22. (CURRENTLY AMENDED) The process of claim 1 wherein:

(a) about 1.2 to 1.4 equivalents of the non-nucleophilic strong base are added to a solution containing:

(i) an equivalent of the compound of formula **V**,

(ii) about 1.0 to about 2.0 equivalents of the compound of formula **X**, and

(iii) about 1.0 to about 4.0 equivalents of the chiral amino alcohol **XI** or **XII**, and

(iv) at least about ~~about~~ 1.0 equivalents of the organic amine or ether additive,

while maintaining the temperature of the so-formed reaction mixture at about 5 °C to about 50 °C;

(b) the mixture from step (a) is cooled to about 0 °C to about 10 °C, and about 0.1 to about 3.0 equivalents of water are added;

(c) an additional about 0.9 to about 1.1 equivalents of the non-nucleophilic strong base are added to the mixture from step (b) while maintaining the temperature at about 0 °C to about 10 °C; and

(d) the temperature of the mixture from step (c) is raised to about 10 °C to about 50 °C and an additional about 1.0 to about 1.5 equivalents of the non-nucleophilic strong base are added while maintaining the temperature at about 10 °C to about 50 °C.

23. (PREVIOUSLY PRESENTED) The process of claim 1 wherein:

(a) about 1.3 equivalents of the non-nucleophilic strong base are added to a solution containing:

(i) an equivalent of the compound of formula **V**,

(ii) about 1.0 to about 1.5 equivalents of the compound of formula **X**, and

(iii) about 1.2 to about 3.5 equivalents of the chiral amino alcohol **XI** or **XII**, and

(iv) about 1.0 to about 4.0 equivalents of the organic amine or ether additive,

while maintaining the temperature of the so-formed reaction mixture at about 10 °C to about 45 °C;

(b) the mixture from step (a) is cooled to about 0 °C to about 5 °C, and about 0.5 to about 1.2 equivalents of water are added;

(c) an additional about 1.0 equivalents of the non-nucleophilic strong base is added to the mixture from step (b) while maintaining the temperature at about 0 °C to about 8 °C; and

(d) the temperature of the mixture from step (c) is raised to about 15 °C to about 45 °C and an additional about 1.1 to about 1.4 equivalents of the non-nucleophilic strong base are added while maintaining the temperature at about 15 °C to about 45 °C.

24. (PREVIOUSLY PRESENTED) The process of claim 1 wherein:

(a) about 1.3 equivalents of the non-nucleophilic strong base are added to a solution containing:

(i) an equivalent of the compound of formula **V**,

(ii) about 1.1 to about 1.3 equivalents of the compound of formula **X**, and

(iii) about 1.3 to about 3.0 equivalents of the chiral amino alcohol **XI** or **XII**, and

(iv) about 1.2 to about 3.0 equivalents of the organic amine or ether additive,

while maintaining the temperature of the so-formed reaction mixture at about 15 °C to about 25 °C;

(b) the mixture from step (a) is cooled to about 0 °C to about 5 °C, and about 0.5 to about 1.0 equivalents of water are added;

(c) an additional about 1.0 equivalents of the non-nucleophilic strong base is added to the mixture from step (b) while maintaining the temperature at about 0 °C to about 8 °C; and

(d) the temperature of the mixture from step (c) is raised to about 15 °C to about 40 °C and an additional about 1.1 to about 1.4 equivalents of the non-nucleophilic strong base are added while maintaining the temperature at about 15 °C to about 40 °C.

25. (PREVIOUSLY PRESENTED) The process of claim 1 wherein the inert organic solvent is selected from the group consisting of: toluene, benzene, cyclohexane, tetrahydrofuran, anisole, chlorobenzene, and mixtures thereof.

26. (PREVIOUSLY PRESENTED) The process of claim 1 wherein the inert organic solvent is selected from the group consisting of: toluene, ethylbenzene and a mixture thereof.

27. (PREVIOUSLY PRESENTED) The process of claim 1 wherein the inert organic solvent is a mixture of toluene and ethylbenzene wherein the v/v ratio of toluene to ethylbenzene ranges from 1:5 to 1:1.

28. (PREVIOUSLY PRESENTED) The process of claim 1 wherein the chiral amino alcohol is quinine, the non-nucleophilic lithium base is lithium di-isopropyl amide, the organic amine or ether additive is 2-isopropylaniline or a 3:1 mixture of N-phenyl, N-

benzyl amine and TMEDA, the solvent is toluene, and water is added after the first addition of lithium di-isopropyl amide; and about 2.0 to about 3.0 additional equivalents of lithium di-isopropyl amide, as lithium di-isopropyl amide –THF, are added in two equal portions.

29. (PREVIOUSLY PRESENTED) The process of claim 1 wherein to a mixture of 1.0 equivalent of compound **V**, 1.2 equivalents of compound **X**, 2.1 equivalents of quinine, and 2.0 equivalents of 2-isopropylaniline, there is sequentially added 2.1 equivalents of lithium di-isopropyl amide –THF (1 to 2 molar in ethylbenzene), 0.7 equivalents of water, and 0.7 equivalents of lithium di-isopropyl amide –THF, wherein the temperature of the so-formed reaction mixture is adjusted to between 15° and 40°C, and a third portion of 1.3 equivalents of lithium di-isopropyl amide -THF is added over a period of 4 to 10 hours.

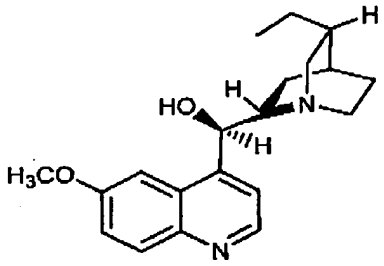
30. (PREVIOUSLY PRESENTED) The process of claim 29 further comprising the crystallization of the acid addition salt formed by contacting the free base **VI** with at least one equivalent of a chiral acid selected from the group consisting of N-α -t-Boc-L-asparagine and N-acetyl-L-phenylalanine

31. (PREVIOUSLY PRESENTED) The process of claim 1 wherein 1.0 equivalent of the lithium di-isopropyl amide-THF in ethylbenzene is pre-mixed with 0.5 equivalents of isopropylaniline, and then to a mixture of 1.0 equivalent of compound **V**, 1.1 equivalents of compound **X**, and 1.5 equivalents of quinine, there is sequentially added 2.1 equivalents of the lithium di-isopropyl amide-THF/2-isopropylaniline base complex, 0.7 equivalents of water, and 0.7 equivalents of lithium di-isopropyl amide-THF/2-isopropylaniline base complex, and the temperature of the mixture is adjusted to between 15° to 40°C, and a third portion of 1.3 equivalents of lithium di-isopropyl amide-THF/2-isopropylaniline base complex is added over 3 to 10 hours.

32. (PREVIOUSLY PRESENTED) The process of claim 31 further comprising the crystallization of acid addition salt formed by contacting the free base **VI** with at least

one equivalent of a chiral acid selected from the group consisting of: N-α-t-Boc-L-asparagine and N-acetyl-L-phenylalanine.

33. (NEW) The process of Claim 1 wherein the chiral amino alcohol is:

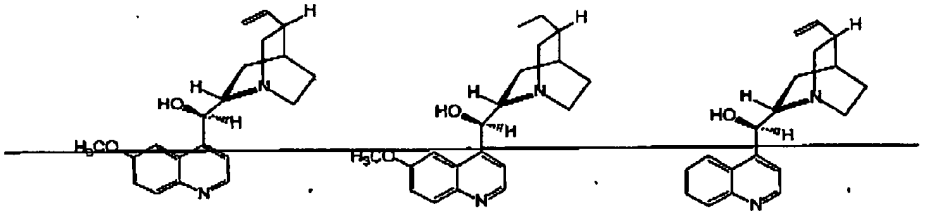



Hydroquinine

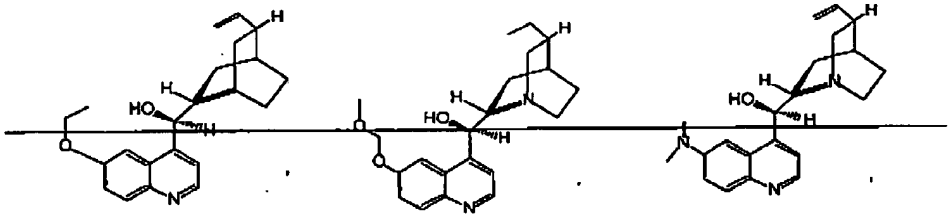
**IN THE SPECIFICATION**

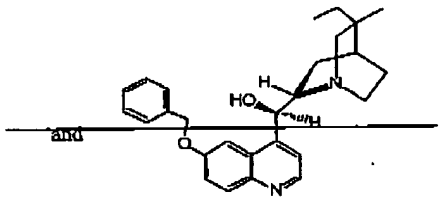
Correct the first full paragraph on page 12 (i.e., lines 5 to 8) to read:

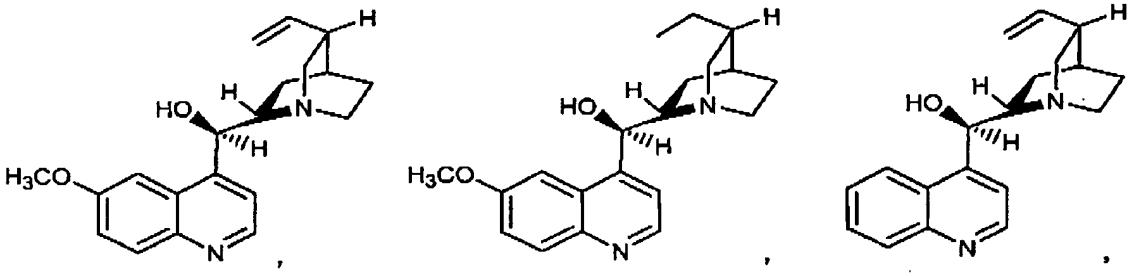
"Non-limiting examples of chiral amino alcohols of formula **XII** include quinine, and the quinine derivatives:



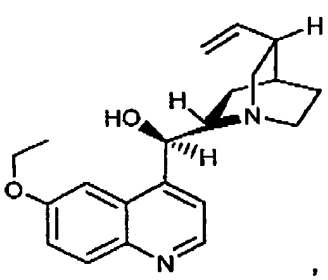
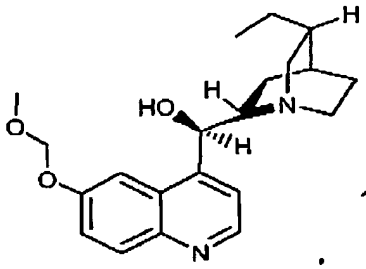
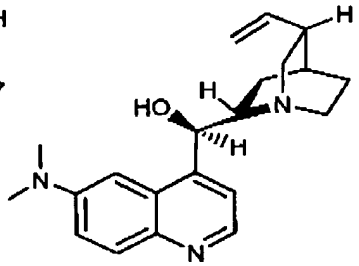
Quinine Hydroquinine (-)-



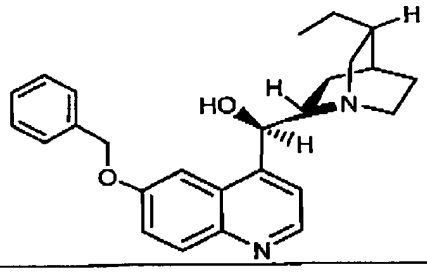




Quinine Hydroquinine

and



."

## REMARKS

The Examiner is invited to telephone the undersigned to discuss any issues deemed remaining after consideration of this amendment.

With the entry of Claim 33, the total number of claims in the present Application is 26, and based on the total number of claims already paid for no fee is deemed due for added Claim 33. The fee sheet filed with Applicants' February 22, 2005 amendment authorized payment for added claims based upon a total of 26 claims when there were only a total of 25 claims. Thus, if Applicants' Deposit Account was charged according to this fee sheet no fee is due for added Claim 33. If, however, a fee is deemed due, then authorization is hereby given to charge any such fee to our Deposit Account No. 19-0365.

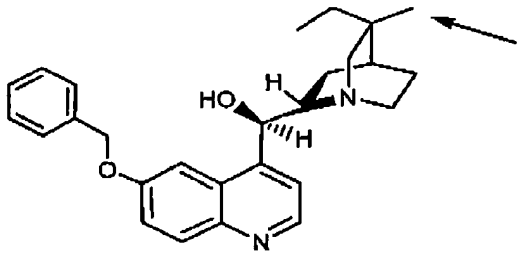
The claims have been amended to better define Applicants' claimed invention and to correct inadvertent errors.

Claim 1 was amended to clarify the structure of formula **XII** in view of the disclosure on the top of page 3.

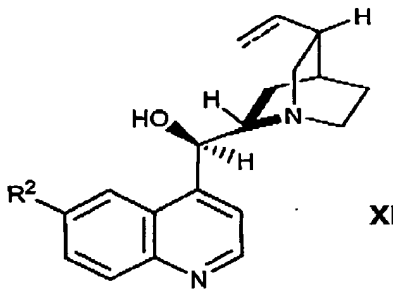
Claim 8 was amended to delete the duplicate "the".

Claim 9 was amended to specify the chiral amino alcohols. Support for this amendement may be found, for example, on page 12. In amending Claim 9 the fragment of the compound name for the last compound in the first line was deleted. This same amendment was made to page 12 of the specification.

Also, in amending Claim 9 based on the description on page 12, as well as in amending the specification on page 12, the last structure was amended to correct an obvious inadvertent error, i.e., the methyl group bound to the bicyclic ring was amended to a H atom. As originally filed, the last structure on page 12 was depicted with a methyl group bound to the bicyclic ring:

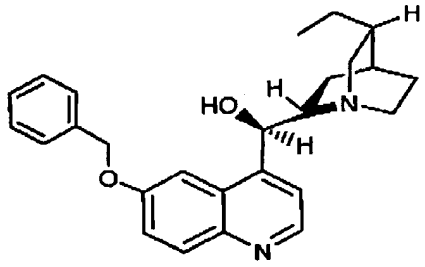


As stated on lines 5 to 6 of page 12, the structures depicted were non-limiting examples of chiral amino alcohols of formula **XII**. Formula **XII**, as depicted on page 3, has a H atom bound to the bicyclic ring:




**XII**

In view of this disclosure, and in view of the H atoms in the first six compounds on page 12, it should be clear that the last structure should have a H atom, and not a methyl group, bound to the bicyclic ring. Therefore, the last structure in Claim 9, as well as the last structure on page 12, has been depicted as:




Claim 20 was amended to make it depend on Claim 1 instead of Claim 17.

Claim 22 was amended to delete the duplicate "about" in Step (a)(iv).

Claim 33 was added. Support for this claim is found in the specification, for example, on page 12 in the first line of compounds, and on page 12 at lines 9 to 11.

The specification was amended as described in the remarks directed to the amendment made to Claim 9.

Claims 2, 3, 4, 14, 15, 16 and 19 were previously cancelled without prejudice.

Claims 8, 9, 20, and 22 have been amended.

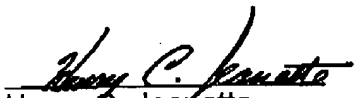
Claims 7, 10, 17, 18, 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, and 32 were previously presented.

Claims 5, 6, 11, 12, and 13 are the originally filed claims.

Claim 33 has been added.

Thus, Claims 1, 5, 6, 7, 8, 9, 10, 11, 12, 13, 17, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 and 33 are in the Application.

Respectfully submitted,



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